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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,076	02/03/2004	Howard F. Bunn	18989-032	5061

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/772,076	BUNN ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *6-8,10,17,22,26-30,38-44 and 54-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9,11-16,18-21,23-25,31-37 and 45-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 August 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-59 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group II (claims 1-5, 9, 11-16, 18-21, 23-25, 31-37, and 45-53), drawn to an in vivo method of increasing insulin production or inhibition of pancreatic cell loss/death, comprising contacting pancreatic islet cells with a flavo-heme oxido-reductase polypeptide or an agonist thereof or more specifically Ncb5or polypeptide, in the reply filed on 11/13/2006 is acknowledged.

Claims 6-8, 10, 17, 20, 26-30, 38-44, and 54-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected non-elected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/13/2006.

Claims 1-5, 9, 11-16, 18-21, 23-25, 31-37, and 45-53 are under consideration.

Information Disclosure Statement

3. The information disclosure statements were filed on 12/2/2004 and 6/14/2005. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Drawings

4. The drawings are objected to under 37 CFR 1.83(a) because they fail to show figures, bar graphs, and information as described in the brief description of the drawings in the specification. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

More specifically, the figures do not correspond to their Brief Descriptions in the Specification. For example, the description of Figure 1 discloses a photograph of a blot (last two lines of p. 5); however, Figure 1 of the drawings, filed 8/9/2004 is a bar graph. Also Figure 4a-h discloses that the comparisons are between WT, HT, KO, however, in

most of these figures only WT and KO are present. Applicant is requested to review all of the figures and make proper revision to assure that the brief descriptions correspond to the drawings.

Claim Objections

5. Claims 1, 15, 31,and 51 are objected to because of the following informalities: These claims encompass non-elected subject matter (i.e.-*in vitro* and *ex vivo* methods). Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

6. Claim(s) 1-5, 31-37, and 45-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instantly claimed method is drawn to a method of increasing insulin production, comprising contacting a pancreatic islet cell with a flavo-heme oxido-reductase polypeptide or an agonist thereof.

When the claims are analyzed in light of the specification, the instant invention encompasses use of a flavor-heme oxido-reductase polypeptide or an agonist thereof. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. While the specification mentions prophetically a flavo-heme oxido-reductase polypeptide or an agonist thereof, the specification fails to disclose any flavo-heme oxido-reductase polypeptide or any agonist thereof other than NADPH cytochrome B5 oxidoreductase, referred to in the specification as Ncb5or. Therefore because the specification only discloses one species, Ncb5or, the specification does not teach the complete structure of a representative number of species of the claimed genus that comprises a flavo-heme oxido-reductase polypeptide or an agonist thereof.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant characteristics, specified features and functional attributes that would distinguish different members of the claimed genus. The specification discloses that a disruption of Ncb5or expression in knockout mice results in insulin deficiency (p. 7, lines 29-30). However, the specification does not discloses any relevant characteristics, specified features and functional attributes that would distinguish different members of the claimed genus, a flavo-heme oxido-reductase polypeptide or an agonist thereof, especially one that would be involved in insulin regulation and diabetes. Therefore, a representative number of species have not been sufficiently described by other relevant characteristics, specified features and functional attributes in the specification as required by the written description requirement.

In conclusion, given the breadth of the genus, species have not been sufficiently described by other relevant characteristics, specified features and functional attributes, and the limited number of examples provided, and given that no specific identifying features/characteristic of species of the genus, were provided, the written description requirement disclosing the complete structure of genus comprising a flavo-heme oxido-reductase polypeptide or an agonist thereof has not been met. Furthermore, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the genus comprising a flavo-heme oxido-reductase polypeptide or an agonist thereof, at the time the application was filed.

Enablement

7. Claims 1-5, 9, 11-16, 18-21, 23-25, 31-37 and 45-53 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is drawn to a method of increasing insulin production, alleviating a symptom of diabetes, increasing serum insulin levels, decreasing serum glucose levels, inhibiting a loss of beta cells in pancreatic islet tissue, and inhibiting cell death, comprising administering or contacting cells, more specifically pancreatic beta cells with a flavo-heme oxido-reductase polypeptide, more specifically the polypeptides of SEQ ID NOS:3, 4, and 5, which are Ncb50r polypeptides, or an agonist thereof.

Narrowing embodiments further specify the method further comprise contacting pancreatic islet cells with an anti-oxidant, more specifically nicotimamide.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification teaches that the basis of this invention is the unexpected discovery that deletion of the oxidoreductase Ncb5or gene leads to insulin deficiency in mice (p. 7, lines 29-30). The specification teaches that Ncb5or is widely expressed in many organs (p. 8, lines 6-7): however, despite its ubiquitous expression, targeted ablation of Ncb5or in mice results in the very specific phenotype of severe diabetes

with pronounced impairment of insulin production in beta cells. Specifically, Ncb5or-/- mice have a phenotype similar to maturity onset diabetes in the young (MODY). Animals up to one month of age have normal blood sugar levels, however by 8 weeks of age the mice develop severe hyperglycemia with marked reduction of plasma insulin. The mice are glucose intolerant and are insulin responsive. The animals have a decrease in white adipose tissue and a reduction of body mass of about 15% compared to the littermate controls. In contrast they have normal amounts of brown adipose. In addition, the animals have an increase in serum trigycerides and serum cholesterol (p. 8, 12-20).

However, the instant invention is not drawn to the disclosed Nbc5or knockout mouse of the inventors. The instant invention is a method of treating symptoms of diabetes by administering a flavor-heme oxido-reductase polypeptide or an agonist thereof, or more specifically Ncb5or. However, neither the specification nor the art teach that treating a diabetes mouse model or a diabetic individual with a flavo-heme oxido-reductase polypeptide or an agonist thereof or more specifically Ncb5or will increase insulin production, alleviate a symptom of diabetes, increase serum insulin levels, decrease serum glucose levels, inhibit a loss of beta cells in pancreatic islet tissue, and inhibiting cell death as claimed.

A knockout mouse such as the Ncb5or knockout mouse disclosed in the specification provides valuable information about the normal physiological role of a gene. Knockout animals are also often invaluable tools for providing models of disease and discovering new therapies. However, an observed phenotype that is the result of a

gene deletion does not mean that treatment of a subject that has similar symptoms with a compound that replaces the deleted gene or its activity will result in an alleviation of the observed phenotype associated with the deletion because it is not clear that the deleted gene is associated with the aberrant function in the world population. Applicant has not established that any or all animals with diabetes or symptoms thereof are lacking Ncb5or activity or that they would benefit from increased NCB5or activity.

To further support this concept in the instant invention, the specification and post-filing art discloses methods for determining if a mutation and variants of the Ncb5or gene are associated with diabetes in human diabetes population. The specification discloses that Ncb5or was not contributing to the NOD mouse diabetes susceptibility (p. 24 lines 22-23). Andersen et al, which includes the instant inventor as coauthors in this publication, indicates that variation in the coding region of Ncb5or is not a major contributor in the pathogenesis of diabetes (Diabetes 53(11):2992-2997, 2004, see abstract). Therefore in both the mouse models and the human diabetes population, it is unclear what role that Ncb5or is playing if any in diabetes and that there are other contributing factors that play a role in diabetes as well. Therefore, a method of treatment of symptoms of diabetes, based on the results of a Ncb5or knockout mouse is overlooking the complexity of involvement other factors or the involvement that Ncb5or may or may not have in aberrant expression of Ncb5or.

Further evidence of uncertainty about the relationship between Ncb50r knockout mice and how its phenotype relates to the disease state of diabetes arise in

consideration of potential deleterious factors that may be contributed to from the background of the transgenic Ncb5or knockout mouse. The specification discloses that the phenotype of Ncb5or -/- animals was studied in three genetic backgrounds: C57BL/6+129, Balb/c+129, and pure 129, prepared by backcrossing chimeric animals with demonstrated germline transmission of the targeted gene into 129 wild type mice. All of the results presented below pertain to male animals with BALB/cAnN; 129 genetic background. The identical diabetic phenotype has also been seen in male and female C57BL/6;129 Ncb5or -/- and 129 Ncb5or -/- animals. None of the BALB/cAnN;129 Ncb5or -/- mice had any abnormalities on gross or microscopic examination or extensive clinical laboratory evaluation except those noted below (p. 20, lines 16-23).

The art teaches that both the C57BL/6 and 129, the strains most commonly used in making knockout animals have a predisposition of hyperinsulinemia, insulin resistance, and other symptoms associated with diabetes. Leiter et al (Diabetologia 45:296-308, 2002) teaches C57BL/6 mice are diabetes susceptible and commonly know to enhance diabetic phenotypes in knockout mice models of diabetes (p. 298, col 2, par 2). Leiter also teaches that the 129 strain genome harbours latent, undefined diabetes susceptibility quantitative trait loci capable of enhancing the deleterious effects of reduced insulin receptor signaling (p. 299, col 1). Leiter et al also teaches a beta-2-microglobulin knockout mouse wherein, B6;129 genetic background admixture was the basis for the observed "autoimmune diabetes" rather than the presence of absence of beta-2-microglobulin gene (p. 300, col 1). Therefore, the art clearly

indicates that the B6, the 129, and the b6/129 cross backgrounds all have the ability to contribute in a diabetes phenotype. Given that this is the background of all the mice expressing a diabetic phenotype, it is unclear to what extent the Ncb50r disruption and or the genetic background contributes to the reported phenotype in the Ncb50r knockout mouse which is the basis of the instant invention.

Further evidence to the uncertainty of the enablement of the instant invention is seen in WO 03/087399 (of record in the IDS). This WO document disclosed a method of treatment of symptoms of diabetes, comprising administering an inhibitor or antagonist of NADPH oxidase or NADPH oxidase complex (p. 7, par 1). They further disclose NADPH oxidase or NADPH oxidase complex can be (b5+b5r) oxidoreductase of SEQ ID NOS: 16 which is homologous to the SEQ ID NOS: 3-5 of the instant application (p. 7, par 8) or a Ncb5or polypeptide. Therefore, since the instant method is a means of enhancing expression of a Ncbor5 or agonize Ncbor5 to alleviate symptoms of diabetes, this is in conflict with the WO 03/087399 which provides an inhibitor to alleviate symptoms of diabetes. Therefore, from the disclosure in the art and the contradictory disclosure in the specification, an artisan would not be certain if the underlying involvement of Ncb5bor is agonistic or antagonistic to aberrant physiological functions associated with diabetes.

Most of the discussion has been limited to the species Ncb5or. However the breadth of the claims are drawn to treatment with a flavo-heme oxido-reductase polypeptide or an antagonist. The specification nor the art discloses other a flavor-heme oxido-reductase polypeptide or an antagonist that are capable of alleviating

symptoms of diabetes. Therefore, an artisan would not know how or if other flavor-heme oxido-reductase polypeptides or an antagonists would relieve symptoms of diabetes.

The breadth of the invention is also drawn to the treatment of any cells. However, the specification and other claims disclose that only insulin producing cells, i.e., beta cells of the pancreas, are involved in the symptoms of diabetes discussed. Therefore an artisan would not know how to alleviate symptoms of diabetes by contacting any other cell than beta cell of the pancreas.

Overall, the instant invention is deemed not to be enabled by the specification because it does not establish a relationship between diabetes and a flavo-heme oxido-reductase polypeptide, more specifically the polypeptide or Ncb5or. The invention is based on a Nbc5or knockout mouse that displays a diabetic phenotype, but the specification can not rule out the diabetic phenotype is not associated with some contribution from other factors such as genetic background. Furthermore, since other inventors suggest treating with inhibitors to Ncb5or to alleviate symptoms which is in direct contradiction to the instant invention, it is not clear that the role of Ncb5or has been established. Therefore, for all of the above disclosed reasons, the instant invention is not enabled.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 11, 18, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 18, 23 recite, "wherein said is an inducer of Ncb5or". The metes and bounds of this recitation are indefinite because it is not clear as to what "said" is referring. The claims are interpreted to read "said compound" to advance prosecution.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 45-48 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/155301 A2 (pub date 8/2/2001; only cited pages are enclosed because the original document is 1180 pages) as evidenced by the SCORE search results notes.

The instant invention is drawn to a method of inhibiting cell death, comprising contacting a cell with a composition comprising a flavo-heme oxido-reductase polypeptide or an agonist thereof (claim 1). Narrowing embodiments specify that the polypeptide comprise SEQ ID NOS: 4 (claim 46), 3 (claims 47), or 5 (claim 48) and that the cell is provided, in vivo, in vitro, or ex vivo (claim 51).

The purpose of this rejection is to demonstrate the breadth of the claims. Given its broadest reasonable interpretation, the claimed method only requires contacting any

cell with a flavo-heme oxido-reductase polypeptide or an agonist thereof regardless of its intended effect (ie inhibiting cell death). Because "inhibiting cell death" is in the preamble and not a limitation of the in the method steps, it does not receive patentable weight. Therefore, if a method disclosing the same method step or whatever purpose will anticipate these claims.

W01/155301 discloses an enormous list of novel polypeptides including SEQ ID NO:1726 which encompasses sequences with 100% homology with SEQ ID NOS:3-5 of the instant application (see SCORE search results notes). W01/155301 discloses that fragments, analogs, and derivatives thereof from SEQ ID NO: 1726 (p. 859, [276]) for therapeutic use and can be used in *in vitro* cell culture assays which a patient tissue sample is grown in culture and exposed to or otherwise administered a compound of SEQ ID NO:1726 (p. 865, [298]). Therefore, because the compound has been administer to a tissue in culture, the compound has been put in "contact" with cells as the claim requires.

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble
AU 1632